UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, DC 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/361,576	07/27/99	STOCKWELL	B	2001180-0028

HM12/1205

BRENDA HERSCHBACH JARRELL
CHOATE HALL & STEWART
EXCHANGE PLACE
53 STATE STREET
BOSTON MA 02109-2891

EXAMINER	
HSU,G	
ART UNIT	**PAPER NUMBER**
1627	13

DATE MAILED: 12/05/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

☆U.S.GOVERNMENT PRINTING OFFICE 1995-319-826

Office Action Summary

Application No.	Applicant(s)
09/361,576	Stockwell et al.
Examiner	**Group Art Unit**
Grac Hsu, Ph.D.	1627

☒ Responsive to communication(s) filed on *Aug 24, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1, 2, 5, 6, 9, 10, 13, 14, 18, 19, 22, and 23* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 5, 6, 9, 10, 13, 14, 18, 19, 22, and 23* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. A Preliminary Amendment and Response to Restriction Requirement, a Response to Second Restriction Requirement, respectively received on May 4, 2000 and August 24, 2000 were entered respectively as Paper Nos. 9 and 11.

Election/Restriction

2. Applicants election, without traverse, in Paper Nos. 9 and 11 of

[1] Group I, claims 1-25; and [2] the following corresponding species for:

[a] species A, claim 9 and 22,
(drawn to the method of claim 1, wherein the step of introducing an assay system capable of undergoing one chemical or biological reaction, the reaction is protein phosphorylation, which includes, but is not limited to protein nucleolin and phosphorylation of histone H3);

[b] species B, claim 6 (introducing at least one eukaryotic cell);

[c] species C, claim 10 (detecting an intracellular event or entity);

[d] species D, claim 14 (providing an assay format containing at least 100 reaction vessels, wherein a volume of each reaction vessel is less than or equal to approximately 200 microliters;

[e] species F, claim 19, (introducing at least one eukaryotic cell); and

[f] species G, claim 23, (detecting an intracellular event or entity).

are acknowledged. Because applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a).

3. Claims 3-4, 7-8, 11-12, 15-17, 20-21 and 24-38 are cancelled as per applicant's request in the May 4, 2000 Response.

4. Claims 39-40 are withdrawn from further consideration by the Examiner under 37 C.F.R. 1.142(b), as being drawn to a non-elected invention, the requirement having not been traversed in Paper No. 9.

Status of Claims

5. Claims 1-2, 5-6, 9-10, 13-14, 18-19 and 22-23 are pending and under examination in the instant application.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first and second paragraphs of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-2, 5-6, 9-10, 13-14, 18-19 and 22-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

[1] screening strategies associated with the following different classes of chemical compounds as affecting aspects of the cell cycle, as indicated by these examples from the instant specification:

[a] Example 6: screen for small molecule suppressors of antiproliferative agents, demonstrated in the cytoblot assay by the simultaneous treatment of mink lung cells with rapamycin and excess FK506, resulting in the ability of cells to incorporate BrdU; wherein said antiproliferative agents are TGF-B, hydroxyurea,

nocodazole, minosine, benomyl, trapoxin, trichostatin and depudicin (see, instant specification page 61-62);

[b] Example 7: screen for natural products suppressors of anti-proliferative agents, obtained from specific marine sponge extracts demonstrated in the cytoblot assay by the simultaneous treatment of mink lung cells with rapamycin and excess FK506, resulting in the ability of cells to incorporate BrdU; wherein said antiproliferative agents, cytostatic proteins or small molecules selected from are TGF-B, hydroxyurea, nocodazole, minosine, benomyl, trapoxin, trichostatin and depudicin and DNA-damaging agents: mitomycin, bleomycin, cisplatin, UV light and gamma irradiation (see, instant specification page 62-63);

[c] Example 9: assaying small molecule suppressors of cell-cycle arresting agents with jugalone, trapoxin and camptothecin (see, instant specification, pages 63-64 ;

[d] Example 10: assaying small molecule suppressors of G-2 arresting agents with purine analogs (see, instant specification, page 65); and

[e] Example 11: use of inventive cytoblot to identify compounds of Formula (1); Formula (20); Formula (30); Formula (40), Formula (50), Formula (60) (see, instant specification at pages 73-81) that alter progression through the mammalian cell cycle, of interfering with the cytoskeletal structure of cells undergoing mitosis (see, instant specification at pages 65-81).

but does not reasonably provide enablement for: [1] ***all*** methods of screening of **all** chemical; [2] the use of ***all*** assay formats; [3] use of ***all*** assay systems as part of the claimed screening method, wherein such assay system include the use of ***all*** chemical or biological reactions compounds for the detection of a desired chemical or biological reaction, property, etc.." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims. .

Factors considered in making such determinations are set forth in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). As discussed below, those factors include, but are

not limited to, the: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) level of one of ordinary skill; (5) level of predictability in the art; (6) amount of direction provided by the inventor; (7) existence of working examples; and (8) quantity of experimentation needed to make or use the invention cased on the disclosure content.

In the present case, [1] the breadth of the claims encompass methods of screening chemical compounds in general. However, the examples in the specification as identified above teach the use of specific classes of compounds in screening for specific chemical or biological activity associated with alteration of the cell cycle, such interference with the cytoskeletal structure of cells undergoing mitosis, to yield positive or negative results; [2] the nature of the invention cannot be determined in light of the foregoing and without knowing the exact compounds and/or generic core structures to be screened for specific chemical or biological activity to be screened in the methods of the instant invention; [3] and [5] the state of the art and the level of predictability in the art cannot be predicted with any certainty what specific test compounds should be used and are likely to provide productive results beyond those compounds tested in Examples 6-7 and 9-11 as taught in the specification; [4] and [6] the inventor provides no guidance beyond the Examples 6-7 and 9-11 taught in the specification as previously mentioned. As a result one of ordinary skill in the art could not predict what other types of test compounds, other those tested in Examples 6-7 and 9-11 as taught in the specification; and [7] and [8] while the existence of working examples are limited to Examples 6-7 and 9-11 as taught in the specification (note that Examples 1-5 are hypothetical examples that do not identify any specific examples to be tested and state only "if test compounds" were used in particular ways,

certain results might be expected) an indeterminate quantity of experimentation would be necessary to determine all potential test compounds to be screened by using the methods of the claimed invention.

In light of the preceding discussion, one skilled in the art ***could not practice*** the claimed invention ***without undue experimentation,*** as claims 1-2, 5-6, 9-10, 13-14, 18-19 and 22-23 fail to correlate reasonably with either the enabling disclosure of the specification and the claims.

8. Claims 1-2, 5, 9-10, 13-14, 18 and 22-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 1 is vague and indefinite in that it recites the following terms: [1] "chemical compounds"; [2] "assay format"; [3]"a plurality of reaction vessels arranged with sufficient density"; [4] "introducing an assay format capable of undergoing at least one chemical or biological reaction"; [5] "detecting an effect of at least one of the chemical compounds on the chemical or biological reaction." It is unclear what the aforementioned generic terms refer to, as the metes and bounds of the aforementioned claims cannot be determined as the specification, claims and art do not recognize to what those generic terms define. Applicants are requested to point to where in the specification each of the aforementioned terms are defined and to amend the claims accordingly to define as taught by Examples 6-7 and 9-11: [1] specific "chemical compounds"; [2] and [4] assay formats and specific chemical or biological reaction the claimed method is directed to (i.e. including specific chemical or biological reactions type(s) and associated assay or screening steps for which the claimed method is directed); [3] what the term

sufficient density means; and [5] how detection is accomplished and what constitutes "an effect of at least one of the chemical compounds on the chemical or biological reaction."

10. Claim 2 is unclear as to applicants intent with respect to the following terms: [1] "a plurality of reaction vessels arranged with sufficient density."; and [2] "no more than about 2 millimeters." It is unclear what the aforementioned terms refer to, as the metes and bounds of the aforementioned claims cannot be determined as the specification, claims and art do not recognize what the generic terms "sufficient density" and "no more than about 2 millimeters" defines. Applicants are requested to point to where in the specification the aforementioned terms are defined and amend the claims accordingly.

11. Claims 5 and 18 unclear as to applicants intent with respect to the following term: "an assay system." It is unclear what the aforementioned term refers to, as the metes and bounds of the aforementioned claims cannot be determined as the specification, claims and art do not recognize what the generic term "assay format" defines. Applicants are requested to point to where in the specification the aforementioned terms are defined and amend the claims accordingly.

12. Claims 9 and 22 are vague and indefinite in that it recites the terms:[1] "the step of introducing an assay system capable of undergoing at least one chemical or biological action"; and [2] "the reaction is selection from the group consisting of . . . and combinations thereof." It is unclear what the aforementioned term refers to, as the metes and bounds of the aforementioned claims cannot be determined as the specification, claims and art do not recognize what the aforementioned generic terms define. For example, what constitutes an assay system, what are the corresponding steps necessary in order to determine how tested compounds of the claims

method are screened, and what biological or chemical reactions are utilized in the aforementioned assay system and what "combinations" of those chemical or biological reactions are used and in what particular order in the "assay system" of the claimed invention. Applicants are requested to point to where in the specification the aforementioned terms are defined and amend the claims accordingly.

13. Claims 10 and 23 are vague and indefinite in that it recites the term: "an intracellular event or entity." It is unclear what the aforementioned term refers to, as the metes and bounds of the aforementioned claims cannot be determined as the specification, claims and art do not recognize what the aforementioned generic terms define. Applicant is requested to point to where in the specification the aforementioned terms are defined and amend the claims accordingly.

14. Claim 14 is vague and indefinite in that it recites the term: [1] "assay format" and [2] "a volume of each reaction vessel is less than or equal to approximately 200 microliters." It is unclear what the aforementioned term refers to, as the metes and bounds of the aforementioned claims cannot be determined as the specification, claims and art do not recognize what the aforementioned generic terms define.

15. Claims 1-2, 5-6, 9-10, 13-14, 18-19 and 22-23 ~~1-6, 27-30, 32-35, 42-48, 50-52, 57-59, 77~~ and ~~85-88~~ do not meet the metes and bounds of the claimed invention as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections.

The omitted structural cooperative relationships relate to the fact that it is unclear from the claimed invention: [1] what is the specific assay system introduced in step 3 of the claimed

method for screening chemical compounds; and [2] what are the associated steps of that assay system and all corresponding chemical or biological reactions that are introduced and/or used in each reaction vessel so that an "effect of at least one if the chemical compounds on the chemical or biological reaction" can or may be detected as required by step 4 of the claimed screening method (including order, connection or attachment is for each of the elements that are necessary to effectuate such a screening purpose, etc.)

Therefore, the metes and bounds of the aforementioned claims cannot be determined as the specification, claims and the art do not recognize a defined set of compounds, active sites or screening methods that define the above-identified generic terms.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1-2, 5-6, 9-10, 13-14, 18-19 and 22-23 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Gallop et al. (U.S. Patent No. 5,525,734, Filed: June 22, 1994, Issued: June 11, 1996), Manns (U.S. Patent No. 4,948,442, Filed June 18, 1995, Issued August 14, 1990), applicants' admission (see, instant specification, page 29, lines 6-19), F.F. Craig ("Chapter 14, Screening Combinatorial Libraries," A Practical Guide to Combinatorial Chemistry, Czarnik and DeWitt, eds., Washington, D.C.: American Chemical Society, 1997, 404).

Gallop et al. teaches: [1] methods for synthesizing and screening pyrrolidine compound libraries via in situ incorporation on a plurality of solid supports or reaction vessels (see, abstract, col. 3, lines 60-67 to col. 4, lines 1-7); [2] that the aforementioned library compounds, such that one unique or single compound per reaction vessel, are screened for biological or pharmaceutical activity (see, col. 4, lines 30-51 and col. 5, lines 41-45) to isolate individual compounds that bind to a receptor (i.e. undergo a biological or chemical reaction) or possess some desired property (see, col. 3, lines 39-41; i.e, such compounds have diverse pharmaceutical and chemical properties/utilities, that include acting as anti-hyperintensive agents, inhibitors of angiotensin-converting enzyme or are included as a central core of biologically active alkaloids or in peptide compounds having receptor binding activity; [3] that the solid supports used herein include other conventional forms (see, col 5, lines 65-68 to col. 6, lines 1-9, esp. col. 6, line 7) or are described in either WO 93/06121 or in the solid supports described in U.S. Patent No. 5,143,854 to screen compounds for binding affinity to ligands (see, col. 3, lines 53-59 and col. 5, lines 65-67 to col. 6, lines 1-9).

In view of the above, Gallop et al. ***differs*** from the claimed invention in that it ***does not teach*** the screening of chemical compounds in an assay format containing a plurality of reaction vessels, which are:

[1] separated from one another by no more than about 5 millimeters;

[2] separated from one another by no more than about 2 millimeters;

[3] that said assay vessel contain at least 100 reaction vessels; and/or

[4] wherein the volume of each reaction vessel is less than or equal to approximately 200 microliters

However, it is conventionally known in the art that assay formats, such as microtiter plates: [a] while commonly used in the standardized form of a multi-well filter apparatus that provides at least 96 depressions or cylindrical wells (see, Manus, col. 1, lines 13-18); [b] it is known "configurations of such assay formats or plates depend upon the wishes of the designer or user (see, Manus, col. 3, lines 53-55)", such configurations include, increasing or decreasing number of wells, materials used in construction, design and structural components of such plates or reaction vessels, including arrangements of, spacing between each well shape or depth (i.e, to be cylindrical, conical), well sample volume; [c] that such plates may be a removable, disposable, or detachable unit for further processing (see, col. 2, lines 45-52) and that such apparatus are commonly used to prepare libraries in microtiter plates via automation or robotics or otherwise (see, Manus, col. 3, lines 53-55 and Craig et al., page 404, lines 1-11); [d] "denser arrays are generally preferred, though it is appreciated that such arrays may desirably have the same external dimensions of a standard 96 well plate in order to facilitate automation using available equipment. Plates containing 384 (Nalge Nunc International, Naperville, IL; Greiner America, Lake Mary, FL) wells have recently become commercially available and may be used in the practice of the present invention. Still denser plates, such as the 6144 well plates . . .are particularly preferred. An ideal assay for high throughput screening would be compatible with any or all of these array formats (see, instant specification, page 29, lines 6-19); and [e] high throughput screening results in the testing of many samples against a number of biological targets

of interest that include compounds derived by automated or manual methods (see, page 399, abstract and lines 1-11 and Craig, p. 401, lines 34-37 to p. 402 to 403) (also see generally, F.F. Craig, "Chapter 14, Screening Combinatorial Libraries," A Practical Guide to Combinatorial Chemistry, Czarnik and DeWitt, eds., Washington, D.C.: American Chemical Society, 1997, 404).

A person of ordinary skill in the art would have been motivated to screen pyrrolidine compounds and/or corresponding compound libraries as taught by Gallop et al. via different assay formats, because the aforementioned compounds and/or corresponding compound libraries as taught by Gallop et al. have diverse pharmaceutical and chemical properties/utilities, etc. it is conventionally known in the art that assay formats, such as microtiter plate or wells are readily adaptable and made to the needs of the designer or used for specific purposes as nessitated by experiment, which may include uses as biological assays or screening, as taught by Manus and F.F. Craig.

In light of the foregoing, a person of ordinary skill in the art would have had a reasonable expectation of success in screening or identifying pharmaceutical pyrrolidine compounds via the use of different assay formats, such as well plate apparatus, because [1] Gallop et al. teaches that synthetic methods for the preparation of pyrrolidine libraries on solid supports and that such compounds have diverse pharmaceutical and chemical properties/utilities; and [2] it is conventionally known in the art that assay formats, such as microtiter plate or wells are readily adaptable and made to the needs of the designer or used for specific purposes as nessitated by experiment, which may include uses as biological assays or screening, as taught by Manus and F.F. Craig.

It would have been ***prima facie*** **obvious** to a person of ordinary skill in the art at the time the invention was made to modify the teachings of Gallop et al. with the teachings of what is conventionally known in the art as taught by Manus and Craig to use different assay formats as adapted to the needs or "wishes of the designer or user" based upon experimental necessity.

18. Claims 1-2, 5-6, 9-10, 13-14, 18-19 and 22-23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zambias et al. (U.S. Patent No. 5,736,412, Filed: May 17, 1996, Issued: April 7, 1998), Manns (U.S. Patent No. 4,948,442, Filed June 18, 1995, Issued August 14, 1990), applicants' admission (see, instant specification, page 29, lines 6-19), applicants' admission (see, instant specification, page 29, lines 6-19), and F.F. Craig ("Chapter 14, Screening Combinatorial Libraries," A Practical Guide to Combinatorial Chemistry, Czarnik and DeWitt, eds., Washington, D.C.: American Chemical Society, 1997, 404).

Zambias et al. teaches: [1] a method directed to the synthesis and/or screening of an array of different organic chemical compounds (see, col. 12, lines 4-7), with a common molecular core structure (see, abstract, col. 9, line 52 and col. 5, lines 31-37); [2] which comprises (see, col. 13, lines 16-18 and 24-25): (a) simultaneous screens for assaying large numbers of parallel compound samples (see, col. 5, lines 1-3) with different structures, functionalities and spatial arrangements for exploring biological activity (see, col. 12, lines 4-7 and examples cols.15-16), such as for use as drug candidates (see col. 11, lines 59-67) in microtiter plates (see, Figure on front of patent); (b) the steps of (1) placing a set of building blocks A in a solvent; (2) mixing the building blocks of A with additional building blocks B; and then mixing the aforementioned solutions with building blocks C in a different solvents, etc. yielding desired products; (3) in which those product

samples are subject to standard organic spectroscopic analysis (see, col. 6, lines 6-21), such as high performance liquid chromatography ("HPLC"), and each sample is analyzed via the removal of aliquot samples from each respective microtiter plate wells (see, also table 4, an expanded view of a single reaction plate layout/template array, col 33, lines 1-20); and [5] to optimize results this method incorporates use of known chemical and physical properties important to set reaction conditions, (i.e., sets of paralogs are constructed by systematically varying five independent parameters: 1 a hydrophobic index; an isoelectric point derived from overall charge by averaging pka and pH values, a hydrophobic moment, an analogous dipole moment, a corrugation factor, etc., See, col. 5, lines 16-30).

In view of the above, Zambias et al. ***differs*** from the claimed invention in that it ***does not teach*** the screening of chemical compounds in an assay format containing a plurality of reaction vessels, which are:

[1] separated from one another by no more than about 5 millimeters;

[2] separated from one another by no more than about 2 millimeters;

[3] that said assay vessel contain at least 100 reaction vessels;

[4] wherein the volume of each reaction vessel is less than or equal to approximately 200 microliters

However, it is conventionally known in the art that assay formats, such as microtiter plates: [a] while commonly used in the standardized form of a multi-well filter apparatus that provides at least 96 depressions or cylindrical wells (see, Manus, col. 1, lines 13-18);

[b] it is known "configurations of such assay formats or plates depend upon the wishes of the designer or user (see, Manus, col. 3, lines 53-55)", such configurations include, increasing or decreasing number of wells, materials used in construction, design and structural components of such plates or reaction vessels, including arrangements of, spacing between each well shape or depth (i.e, to be cylindrical, conical), well sample volume; [c] that such plates may be a removable, disposable, or detachable unit for further processing (see, col. 2, lines 45-52) and that such apparatus are commonly used to prepare libraries in microtiter plates via automation or robotics or otherwise (see, Manus, col. 3, lines 53-55 and Craig et al., page 404, lines 1-11); [d] "denser arrays are generally preferred, though it is appreciated that such arrays may desirably have the same external dimensions of a standard 96 well plate in order to facilitate automation using available equipment. Plates containing 384 (Nalge Nunc International, Naperville, IL; Greiner America, Lake Mary, FL) wells have recently become commercially available and may be used in the practice of the present invention. Still denser plates, such as the 6144 well plates . . .are particularly preferred. An ideal assay for high throughput screening would be compatible with any or all of these array formats (see, instant specification, page 29, lines 6-19); and [e] high throughput screening results in the testing of many samples against a number of biological targets of interest that include compounds derived by automated or manual methods (see, page 399, abstract and lines 1-11 and Craig, p. 401, lines 34-37 to p. 402 to 403) (also see generally, F.F. Craig, "Chapter 14, Screening Combinatorial Libraries," A Practical Guide to Combinatorial Chemistry, Czarnik and DeWitt, eds., Washington, D.C.: American Chemical Society, 1997, 404);

A person of ordinary skill in the art would have been motivated to screen chemical compounds and/or corresponding compound libraries as taught by Zambias et al. via different assay formats, because the aforementioned compounds and/or corresponding compound libraries as taught by Zambias et al. have diverse pharmaceutical and chemical properties/utilities, etc. it is conventionally known in the art that assay formats, such as microtiter plate or wells are readily adaptable and made to the needs of the designer or used for specific purposes as nessitated by experiment, which may include uses as biological assays or screening, as taught by Manus and F.F. Craig.

In light of the foregoing, a person of ordinary skill in the art would have had a reasonable expectation of success in screening or identifying pharmaceutical pyrrolidine compounds via the use of different assay formats, such as well plate apparatus, because [1] Zambias et al. teaches that synthetic and screening methods of chemical compounds and/or libraries that have diverse pharmaceutical and chemical properties/utilities; and [2] it is conventionally known in the art that assay formats, such as microtiter plate or wells are readily adaptable and made to the needs of the designer or used for specific purposes as nessitated by experiment, which may include uses as biological assays or screening, as taught by Manus and F.F. Craig.

It would have been ***prima facie*** **obvious** to a person of ordinary skill in the art at the time the invention was made to modify the teachings of Zambias et al. with the teachings of what is conventionally known in the art as taught by Manus and Craig to use different assay formats as adapted to the needs or "wishes of the designer or user" based upon experimental necessity.

19. Claims 1-2, 5-6, 9-10, 13-14, 18-19 and 22-23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Godowski et al. (U.S. Patent No. 6,025,145, Filed: January 20, 1995 (371 Date), PCT Filed: November 18, 1994 (PCT Priority), Issued: February 15, 2000), Manns (U.S. Patent No. 4,948,442, Filed June 18, 1995, Issued August 14, 1990), applicants' admission (see, instant specification, page 29, lines 6-19), applicants' admission (see, instant specification, page 29, lines 6-19), and F.F. Craig ("Chapter 14, Screening Combinatorial Libraries," A Practical Guide to Combinatorial Chemistry, Czarnik and DeWitt, eds., Washington, D.C.: American Chemical Society, 1997, 404).

Godowski et al. teaches: [1] an kinase receptor activation (KIRA) assay for measuring activation (i.e., autophosphorylation, which is involved in a mechanism of signal transduction in animals) of a tyrosine kinase receptor of interest (see, abstract), wherein ; [2] wherein said assay is a high throughput assay for the evaluation of large numbers of sample test compound ligands, agents etc. and is used for measuring autophosphorylation of the kinase domain of a receptor protein tyrosine kinase (rPTK) using a kinase receptor activation, enzyme-linked immunosorbent assay (KIRA ELISA) (see, col. 1, lines 12-17) and enables identification of agonist and antagonist ligands for the tyrosine receptor of interest; [3] wherein said assay system is conducted in an microtiter plate containing wells, such that: [a] in a first step: a first solid phase (e.g., a/each well of a first assay plate) is coated with a substantially homogeneous population of cells (i.e., usually a mammalian cell line or eukaryotic cell line) so that the cells adhere to the first solid phase (i.e, the cells have either an endogenous tyrosine kinase receptor or have been transformed with DNA encoding a receptor or "receptor construct" and the DNA has been expressed so that the receptor

or receptor construct is presented in the cell membranes of the cells) (see, col. 4, lines 55-59); [b] in a second step: a ligand or analyte is then added to the solid phase having the adhering cells, such that the tyrosine kinase receptor is exposed to the ligand (in each well); [c] Following exposure to the ligand, the adherent cells are solubilized, thereby releasing cell lysate.; [d] A second solid phase is coated with a capture agent which binds specifically to the tyrosine kinase receptor, or, in the case of a receptor construct to the flag polypeptide.; [e] The cell lysate obtained in step c) is added to the wells containing the adhering capture agent so as to capture the receptor or receptor construct to the wells. (i.e., ELISA component of the assay system (see, col.; 5, lines 51-68, to col. 6, lines 1-24); [f] A washing step is then carried out, so as to remove unbound cell lysate, leaving the captured receptor or receptor construct.; [g] The captured receptor or receptor construct is exposed to a labeled anti-phosphotyrosine antibody which identifies phosphorylated residues in the tyrosine kinase receptor.; and [h] Binding of the anti-phosphotyrosine antibody to the captured receptor or receptor construct is measured.

In view of the above, Godowski et al. ***differs*** from the claimed invention in that it ***does not teach*** the screening of chemical compounds in an assay format containing a plurality of reaction vessels, which are:

[1] separated from one another by no more than about 5 millimeters;

[2] separated from one another by no more than about 2 millimeters;

[3] that said assay vessel contain at least 100 reaction vessels;

[4] wherein the volume of each reaction vessel is less than or equal to approximately 200 microliters

However, it is conventionally known in the art that assay formats, such as microtiter plates: [a] while commonly used in the standardized form of a multi-well filter apparatus that provides at least 96 depressions or cylindrical wells (see, Manus, col. 1, lines 13-18); [b] it is known "configurations of such assay formats or plates depend upon the wishes of the designer or user (see, Manus, col. 3, lines 53-55)", such configurations include, increasing or decreasing number of wells, materials used in construction, design and structural components of such plates or reaction vessels, including arrangements of, spacing between each well shape or depth (i.e, to be cylindrical, conical), well sample volume; [c] that such plates may be a removable, disposable, or detachable unit for further processing (see, col. 2, lines 45-52) and that such apparatus are commonly used to prepare libraries in microtiter plates via automation or robotics or otherwise (see, Manus, col. 3, lines 53-55 and Craig et al., page 404, lines 1-11); [d] "denser arrays are generally preferred, though it is appreciated that such arrays may desirably have the same external dimensions of a standard 96 well plate in order to facilitate automation using available equipment. Plates containing 384 (Nalge Nunc International, Naperville, IL; Greiner America, Lake Mary, FL) wells have recently become commercially available and may be used in the practice of the present invention. Still denser plates, such as the 6144 well plates . . .are particularly preferred. An ideal assay for high throughput screening would be compatible with any or all of these array formats (see, instant specification, page 29, lines 6-19); and [e] high throughput screening results in the testing of many samples against a number of biological targets of interest that include compounds derived by automated or manual methods (see, page 399, abstract and lines 1-11 and Craig, p. 401, lines 34-37 to p. 402 to 403) (also see generally, F.F.

Craig, "Chapter 14, Screening Combinatorial Libraries," A Practical Guide to Combinatorial Chemistry, Czarnik and DeWitt, eds., Washington, D.C.: American Chemical Society, 1997, 404).;

A person of ordinary skill in the art would have been motivated to screen agonist and antagonist ligands as taught by Godowski et al. via different assay formats, because [1] Godowski teaches that an kinase receptor activation (KIRA) assay for measuring autophosphorylation, which is involved in a mechanism of signal transduction in animals, of a tyrosine kinase receptor of interest and enables identification of agonist and antagonist ligands for the tyrosine receptor of interest; and [2] it is conventionally known in the art that assay formats, such as microtiter plate or wells are readily adaptable and made to the needs of the designer or used for specific purposes as nessitated by experiment, which may include uses as biological assays or screening, as taught by Manus and F.F. Craig.

In light of the foregoing, a person of ordinary skill in the art would have had a reasonable expectation of success in screening or identifying pharmaceutical pyrrolidine compounds via the use of different assay formats, such as well plate apparatus, because [1] Godowski teaches that an kinase receptor activation (KIRA) assay for measuring autophosphorylation, which is involved in a mechanism of signal transduction in animals, of a tyrosine kinase receptor of interest and enables identification of agonist and antagonist ligands for the tyrosine receptor of interest; and [2] it is conventionally known in the art that assay formats, such as microtiter plate or wells are readily adaptable and made to the needs of the designer or used for specific purposes as nessitated by

experiment, which may include uses as biological assays or screening, as taught by Manus and F.F. Craig.

It would have been ***prima facie*** **obvious** to a person of ordinary skill in the art at the time the invention was made to modify the teachings of Godowski et al. with the teachings of what is conventionally known in the art as taught by Manus and Craig to use different assay formats as adapted to the needs or "wishes of the designer or user" based upon experimental necessity.

Status of Claims

20. No claims are allowed in the above-identified application.

Conclusion

21. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Grace C. Hsu, Ph.D., J.D. whose telephone number is (703) 308-7005. The Examiner may be reached during normal business hours, Monday through Friday from 8:30 am to 6:00 pm (EST). A message may be left on the Examiner's voice mail.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Jythosna Venkat, Ph.D., may be reached at (703) 308-2439. The fax number assigned to Group 1627 is (703) 305-4242. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1627 receptionist whose telephone number is (703) 308-0196.

Grace C. Hsu, Ph.D.
December 4, 2000

DR. JYOTHSNA VENKAT PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600